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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Paper No. 18

Application Number: 09/859,503
Filing Date: May 18, 2001
Appellant(s): MCKENNON ET AL.

Willem F. Gadiano
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed Jun 9, 2003.

*(1) Real Party in Interest*

A statement identifying the real party in interest is contained in the brief.

*(2) Related Appeals and Interferences*

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

*(3) Status of Claims*

The statement of the status of the claims contained in the brief is correct.

*(4) Status of Amendments After Final*

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

*(5) Summary of Invention*

The summary of invention contained in the brief is correct.

*(6) Issues*

The appellant's statement of the issues in the brief is correct. Of these two were resolved with the amendment filed with the Appeal Brief, and a third was dropped by the examiner.

*(7) Grouping of Claims*

Appellant's brief includes a statement that all claims do not stand or fall together and provides reasons as set forth in 37 CFR 1.192(c)(7) and (c)(8). However, reasons are not presented for every individual claim.

*(8) Claims Appealed*

The copy of the appealed claims contained in the Appendix to the brief is correct.

*(9) Prior Art of Record*

1. Cytokines, http://home.attbi.com/~bkrentzman/misc/how.things.work/dna.transcription/cytokines.html downloaded from the Internet 10/25/02

2. Chemokines, Horst Ibelgaufts' COPE: Cytokines Online Pathfinder Encyclopaedia, http://www.copewithcytokines.de/cope.cgi?001668 downloaded from the Internet 10/25/02

3. National Psoriasis Foundation "News & Notices" http://www.psoriasis.org/enbrel.approval.jan02.htm downloaded from the Internet 10/25/02

4. "Centocor Places Congestive Heart Failure Clinical Program On Hold" http://www.jnj.com/news/jnj_news/20020329_0810.htm downloaded from the Internet 10/25/02

*(10) Grounds of Rejection*

The following ground(s) of rejection are applicable to the appealed claims:

Enablement of the Method of Use

Claims 19-25 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Pursuant to *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), one considers the following factors to determine whether undue experimentation is required: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. Some experimentation is not fatal; the

issue is whether the amount of experimentation is "undue"; see *In re Vaeck*, 20 USPQ2d 1438, 1444. The analysis is as follows:

(1) Breadth of claims:

a) Scope of method. The scope is colossal. It covers inhibiting any activity, desired or undesired, mediated by any cytokine, without further limitation (see page 20, lines 27-30). It thus probably covers inhibiting most normal cellular processes and probably covers inhibiting most diseases. Indeed, quite possibly it covers nearly all diseases and cellular processes.

That is, the wording of "inhibiting an activity mediated by a cytokine" means not only inhibiting the vast array of undesired activities caused by cytokines, but also inhibiting desired activities caused by cytokines. Cytokines, after all, are in the body for a reason; the body could not function without their vast array of necessary activities.

Cytokines are extraordinarily diverse in their structure and function. The term cytokine is used as a generic name for a diverse group of soluble proteins and peptides which act as humoral regulators and which, either under normal or pathological conditions, modulate the functional activities of individual cells and tissues. These proteins also mediate interactions between cells directly and regulate processes taking place in the extracellular environment.

As for structure, most Cytokines are unrelated in terms of sequence.

Some attempts have been made to organize cytokines along lines of function, which show the tremendous variety of what is covered by "cytokine". For example, one category is chemokines, a generic name given to a family of activation-inducible Cytokines. Chemokines act as a kind of lure (chemoattractant) and as also as activators

of some types of leukocytes. They have been found to be involved in allergic responses, autoimmune diseases, angiogenesis, inflammation, tumor growth, hematopoietic development, and infectious diseases, especially HIV infection. They play an important role coordinating the movement of T cells, B cells and dendritic cells necessary to generate an immune response. Cells which respond to these are Neutrophils, Eosinophils, Basophils, Monocytes, Resting T cells, Activated T cells, Natural Killer cells, Dendritic cells and B cells. There are at present seventeen known receptors for these cytokines, and many of these receptors exhibit promiscuous binding properties whereby several different chemokines can signal through the same receptor. These cytokines include a) SIS family such as SIS-alpha, SIS-gamma and SIS-epsilon, b) SIG family including JE, KC, MGSA (melanoma growth stimulatory activity), PF4 (platelet factor-4), PBP (platelet basic protein), LDCF (lymphocyte-derived chemotactic factor), RANTES, and SMC-CF, c) SCY family including SCY A1, SCY A2, SCY A3, SCY A4, SCY A5, SCY A6, SCY A7, SCY A8, SCY A9, SCY A10, SCY A11, SCY A12, SCYA13, SCY A14, SCY A15, SCY A16, SCY A17, SCY A18, SCY A19, SCY A20, SCY A21, SCY A22, SCY A23, SCY A24, SCY A25, SCY A26 and many others as well. Other Chemokines include Eotaxin-1, Eotaxin-2, MCP-1, MCP-1a, MCP-1b, MCP-2, MCP-3, MIP-3b (ELC), MCP-4; MCP-5, MIP-1a; HCC-1, IL-8, GCP-2; Gro-a, Gro-b, Gro-g; ENA-78; NAP-2; LIX, MDC, TARC, I-309, Fractalkine, SDF-1, TECK, SLC (6Ckine, Exodus-2), Lymphotactin, SDF-1, PARC, DC-CK1, IP-10, MIG, I-TAC, MIP-3a (LARC, Exodus-1) and BCA-1 (BLC). There are other ways of classifying cytokines, and most have multiple names, as they are discovered in different ways and sometimes named on the basis of different properties.

Another category is Motogenic cytokines, a category Cytokines that influence the motility and migration of cells in ways other than affected by chemotactic processes. The collective term is a functional definition as there is no structural basis that would allow different factors to be classified as motogenic cytokines. Examples include AAMP (Angio-associated migratory cell protein), Adrenomedullin, AMF (autocrine motility factor), ATX (autotaxin), B16-F1 melanoma autocrine motility factor, DF (dissociation factor), Epitaxin, FDMF (fibroblast-derived motility factor), FMSF (fibroblast motility-stimulating factor) ISF (invasion stimulating factor), Ladsin, Monocyte-derived scattering factor, MSF (migration stimulating factor), PDMF (pancreatic cancer-derived motility factor), SF (scatter factor), SFL (scatter factor-like), and Vitronectin.

Another category is the B-cell growth factor (BCGF), which includes CD23, IL-1, IL-2, IL-4, IL-5, IL-6, IL-14, IFN-gamma, α-TNF and β-TNF.

Another type is the colony stimulating factors, which regulate white blood cell production and orchestrate the control of the growth and differentiation of bone marrow progenitor cells. These include M-CSF (macrophage-specific), G-CSF (granulocyte-specific), GM-CSF (macrophage/granulocyte-specific), IL3 (multifunctional), IL-7 and Stem Cell Factor (SCF) and MEG-CSA (megakaryocyte-specific).

A large category of cytokines is the angiogenisis factors, which include aFGF, ANF, Angiogenin, Angiotropin, AtT20-ECGF, B61, bFGF, CAM-RF, ChDI, CLAF, ECGF, ECI, EDMF, EGF, EMAP, Neurothelin, Endostatin, Endothelial cell growth inhibitor, Endothelial cell-viability maintaining factor, Epo, FGF-5, IGF-2, HBNF, HGF, HUAF, IFN-gamma, IL-1, K-FGF, LIF, MD-ECI, MECIF, Oncostatin M, PD-ECGF, PDGF, PF4, PlGF, Prolactin, TNF-alpha, TNF-beta, Transferrin, VEGF, and others.

There are many, many other cytokines, including 9E3, IL-9, IL-10, IL-11, IL-12, IL-13, IL-15 through (at present) IL-29. New ones are being constantly discovered.

b) Scope of compounds employed. In addition, the scope of the compounds themselves is very large. There are four variables each with a substantial number of choices for what these variables can be. Moreover, many of these choices are themselves very broad, such as "heterocyclic". Claim 1 and claim 37 each cover billions of compounds.

(2) The nature of the invention and predictability in the art: The invention is directed toward the action of cytokines and is therefore physiological in nature. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(3) Direction or Guidance: That provided is very limited value, except to make clear what a broad range of disorders is involved. Page 10-11 provides a immense list of disorders, including some very broad categories such as "Inflammatory diseases or disorders" (of which there are hundreds), and "autoimmune diseases" The dosage range information is as broad as a million fold range (page 42 line 32) and is generic as to the particular disease. That is, it is not linked to any particular disorder. These disease categories set forth are extremely diverse. For example, the "Inflammatory diseases or disorders" would presumably include, just as examples, Otitis media, Cystitis, Preseptal cellulitis, Cholecystitis, gout, Sinusitis Pharyngitis, Prostatitis, Cystic fibrosis (CF), Thyroiditis, Regional enteritis (Crohn's disease or ileitis),Osteomyelitis, Dacryoadenitis,

Conjunctivitis, Rheumatoid arthritis, Adult (or Acute) Respiratory Distress Syndrome (ARDS), Chronic bronchitis, Acute bronchitis, Asthma, Myocarditis, Glossitis, Meningitis, Myelitis, Dactylitis, Inclusion body myositis, Encephalitis, Hepatitis, Hemorrhoids, frostbite injury, bacterial meningitis, acute airway inflammation, allograft rejection, hemorrhagic shock, septic shock, ischemia reperfusion injuries, Urethritis, eruption of teeth in a child (teething), Inflammation of the nails, Bright's disease (or glomerulonephritis), bronchiolitis, alveolitis, vasculitis, idiopathic pulmonary fibrosis, bronchiolitis obliterans, histiocytosis X, chronic eosinophilic pneumonia, granulomatous vasculitis, Goodpasture's syndrome, pulmonary alveolar proteinosis, asbestosis, coal worker's pneumoconiosis, silicosis, byssinosis, aluminosis, anthracosis, asbestosis, chalicosis, siderosis, tabacosis, hypersensitivity pneumonitis, Pulmonary Sarcoidosis Bronchiectasis, Stomatitis, mucositis, aphthous ulcers, Acute Necrotizing Ulcerative Gingivitis i.e. "trench mouth", Lichen Planus, Rhinitis, Wegener's Granulomatosis, Pancreatitis, Neuroretinitis, River blindness, scleritis, Pneumonia, Blepharitis, Dacryocystitis, episcleritis, choroiditis, uveitis, Atrophic gastritis, Erosive (hemorrhagic) gastritis, appendicitis, sunburn, reaction to ticks or bee string, acute allergic contact dermatitis (such as poison ivy), pili incarnati, Acne, and many more. Known autoimmune disorders include multiple sclerosis, autoimmune uveitis, rheumatoid arthritis, Addison's disease, thyroiditis, atrophic gastritis, myasthenia gravis, idiopathic thrombocytopenic purpura, hemolytic anemia, systemic lupus erythematosus, primary biliary cirrhosis, Wegener's granulomatosis, polyarteritisnodosa, erythema nodosum leprosum, autoimmune uveitis, Guillain-Barré syndrome (GBS), allergic encephalomyelitis, acute necrotizing hemorrhagic encephalopathy, idiopathic bilateral

progressive sensorineural hearing loss, aplastic anemia, pure red cell anemia, polychondritis, scleroderma, Stevens-Johnson syndrome, idiopathic sprue, lichen planus, Crohn's disease, Graves ophthalmopathy, sarcoidosis, primary biliary cirrhosis, type I diabetes, autoimmune optic neuritis, uveitis posterior, or interstitial lung fibrosis, alopecia, Sjogren's Syndrome, Goodpasture Syndrome, Myasthenia Gravis, inflammatory bowel disease and many more.

(4) State of the Prior Art. So far as the examiner is aware, pyridopyrimidine triones have not been used as cytokine regulatory pharmaceuticals. In fact, the entire area of agents designed to regulate cytokines is extremely new, although it is quite possible that some medicines operate that way without that being understood at the time the medicine was first used. Almost all Cytokines are pleiotropic effectors showing multiple biological activities. In addition, multiple cytokines often have overlapping activities and a single cell frequently interacts with multiple cytokines with seemingly identical responses (cross-talk). One of the consequences of this functional overlap is the observation that one factor may frequently functionally replace another factor altogether or at least partially compensate for the lack of another factor. Since most Cytokines have nearly ubiquitous biological activities, their physiologic significance as normal regulators of physiology is often difficult to assess. The activities of cytokines as a group are extremely complex. Many Cytokines show stimulating or inhibitory activities and may synergize or antagonize also the actions of other factors. A single cytokine may elicit reactions also under certain circumstances which are the reverse of those shown under other circumstances. The type, the duration, and also the extent of cellular activities induced by a particular cytokine can be influenced considerably by the micro-

environment of a cell, depending, for example, on the growth state of the cells (sparse or confluent), the type of neighboring cells, cytokine concentrations, the combination of other Cytokines present at the same time, and even on the temporal sequence of several Cytokines acting on the same cell. The responses elicited by Cytokines are therefore contextual and the "informational content", i.e. the intrinsic activities of a given cytokine may vary with conditions.

(5) Working Examples: Example 12 and both examples 11 show that most (but not all) of the compounds tested suppress IL-4 or IL-12 signaling, or both. These are just a tiny portion of the cytokines embraced, and these examples do not demonstrate that these compounds have any *in vivo* properties, as these are *in vitro* tests. These two, IL-4 and IL-12, are such a tiny proportion of the entire population of cytokines that they cannot possibly representative of cytokines generally.

(6) Skill of those in the art: The skill level in the art is low, relative to the complexity of task (see point A below). In general Cytokines act on a wider spectrum of target cells even than hormones and, unlike hormones, Cytokines are not produced by specialized cells which are organized in specialized glands, i.e. there is not a single organ source for these mediators. The fact that cytokines are secreted proteins also means that the sites of their expression do not necessarily predict the sites at which they exert their biological function. Most cytokines are of unknown, or little known, function. There is no clear idea how many cytokines there are, as new ones are being discovered all the time. Except for a very few, regulation of the cytokines is a very poorly understood area.

(7) The quantity of experimentation needed: Extensive experimentation will be needed, particularly because of factors 1), 4), 5) and 6) above; see point A and F below. This is in

part because of the vast scope and complexity of this area. More extensive experimentation than normal is needed because it is already established for at least one cytokine (α-TNF, one of the most extensively studied cytokines) that sometimes suppressing it makes matters worse when one would have expected better. That is, Tuberculosis and MS clearly have α-TNF activation, but the α-TNF antagonist Remicade has been shown to make matters worse for these. Likewise, while α-TNF has a role in congestive heart failure, patients with CHF are now told to avoid using Remicade because testing showed it to be worse than placebo.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

The traverse is unpersuasive.

A. Appellants initially ask for evidence to support the examiner's characterization of cytokines, saying "Nothing that the examiner has discussed is referenced to any documents of record in the application file." First, this information is known to one of ordinary skill in the art, and Appellants have not disputed the accuracy of any of what the examiner has said. Moreover, the examiner has cited the Cytokines, http://home.attbi.com/~bkrentzman/misc/how.things.work/dna.transcription/cytokines.html reference, which states in part, "Today the term cytokine is used as a generic name for a diverse group of soluble proteins and peptides which act as humoral regulators ...

and which, either under normal or pathological conditions, modulate the functional activities of individual cells and tissues. These proteins also mediate interactions between cells directly and regulate processes taking place in the extracellular environment ...Some cytokines also behave like classical hormones in that they act at a systemic level, affecting, for example, biological phenomena such as inflammation , systemic inflammatory response syndrome , and acute phase reaction , wound healing , and the neuroimmune network . In general, cytokines act on a wider spectrum of target cells than hormones... cytokines are not produced by specialized cells which are organized in specialized glands, i.e. there is not a single organ source for these mediators. The fact that cytokines are secreted proteins also means that the sites of their expression does not necessarily predict the sites at which they exert their biological function...Most cytokines were detected initially in functional tests in vitro as biochemically undefined activities or as distinct factors with distinct biological activities...One should be aware of the fact that at this moment in time *the relevance of many in vitro activities of cytokines to their endogenous functions within an intact organism is not clearly defined. Almost all cytokines are pleiotropic effectors showing multiple biological activities.* In addition, multiple cytokines often have overlapping activities and a single cell frequently interacts with multiple cytokines with seemingly identical responses (cross-talk). One of the consequences of this functional overlap is the observation that one factor may frequently functionally replace another factor altogether or at least partially compensate for the lack of another factor. Since *most cytokines have ubiquitous biological activities*, their physiologic significance as normal regulators of physiology is often difficult to assess...Many cytokines show stimulating or

inhibitory activities and may synergise or antagonize also the actions of other factors. *A single cytokine may elicit reactions also under certain circumstances which are the reverse of those shown under other circumstances.* The type, the duration, and also the extent of cellular activities induced by a particular cytokine can be influenced considerably by the micro-environment of a cell, depending, for example, on the growth state of the cells (sparse or confluent), the type of neighboring cells, cytokine concentrations, the combination of other cytokines present at the same time, and even on the temporal sequence of several cytokines acting on the same cell. Under such circumstances combinatorial effects thus allow a single cytokine to transmit diverse signals to different subsets of cells.... The responses elicited by cytokines are therefore contextual and the "informational content", i.e. the intrinsic activities of a given cytokine may vary with conditions. Although a variety of cytokines are known to share at least some biological effects the observations that single cells usually show different patterns of gene expression in response to different cytokines can be taken as evidence for the existence of cytokine receptor-specific signal transduction pathways....The processes responsible for the regulation of cytokines are not well understood. ...Frequently one observes a hierarchical order of cytokine actions with some early Cytokines preactivating cells so that they then can respond to late-acting cytokines ...A close examination of the physiological and pathological effects of the regulated or deregulated ... expression of cytokines in complex organisms has shown that *these mediators are involved in virtually all general systemic reactions of an organism ... including such important processes as the regulation of immune responses ..., inflammatory processes ... hematopoiesis ... and wound healing... Cytokines are*

*important mediators involved in embryogenesis and organ development ... and their activities in these processes may differ from those observed postnatally. In addition they play a key role in neuroimmunological, neuroendocrinological, and neuroregulatory processes ... Cytokines are important positive or negative regulators of mitosis ... differentiation, migration ... cell survival and cell death .. and transformation* ... It has been shown that a number of viral infectious agents exploit the cytokine repertoire of organisms to evade immune responses of the host. Virus-encoded factors ... appear to affect the activities of cytokines in at least four different ways... Cytokines themselves rarely are related closely among each other in terms of primary Sequences..." Emphasis in italics added; these portions in particular especially support the examiner's characterizations. This clearly supports the examiner's statements. In addition, there was cited the Chemokines, Horst Ibelgaufts' COPE: Cytokines Online Pathfinder Encyclopaedia, http://www.copewithcytokines.de/cope.cgi?001668 reference. This covers just a single category of cytokines, the chemokines. This shows that there are literally hundreds of chemokines just in this category alone.

B. Appellants argue that Claim 19 is not limited to any particular cytokine or activity. Agreed.

C. With regard to Wands factor (2), Appellants argue (page 21, line 1) "the unpredictability of the physiological activity of a cytokine is not at issue in the method recited base claim 19". This is not agreed with. This unpredictability is surely a factor in determining enablement. The greater the unpredictability of the particular physiological activity, the less compounds can be deemed enabled, especially in a circumstance where

there is only in vitro testing, and in the circumstance where the category (cytokines) is so diverse in structure and function.

D. With regard to Wands Factor (3), Appellants argue that there is "sufficient guidance" and point to example 11. But as noted, examples 11 and 12 cover only IL-4 or IL-12. They measured only Th1 or T1 cell differentiation. This is only a minuscule proportion of what the claims cover, in terms of both the cytokines themselves, and the processes that they mediate, and cannot be representative of the whole. Appellants argue that there "is no requirement that there be working examples for each class or category..." The examiner makes no such requirement. But there is some requirement of representativeness. The examiner has set forth the extreme diversity of cytokines and what they do, and thus these two *in vitro* tests cannot be deemed representative. In this regard, Appellants on page 22 declare this to be "a simple matter" and "not rocket science". This ignores the fact that the "activity" of the claims covers a vast array of diseases and normal physiological activities, many of which are very poorly understood.

E. With regard to Wands factor (4), when the examiner has said, "So far as the examiner is aware, pyridopyrimidine triones have not been used as cytokine regulatory pharmaceuticals", Appellants reply that the examiner has presented no evidence. Obviously, a negative cannot be proven; if Appellants disagree, they have been invited to provide a counterexample. Also in discussing the state of the art, Appellants state that the examiner presented no evidence for statements like the fact that many cytokines are of little known function, etc., or that new ones are being discovered all the time. However, Appellants do not dispute the accuracy of any of these statements. Surely, Appellants are not going to argue that new cytokines are no longer being discovered!

And note that the above quote says, "at this moment in time *the relevance of many in vitro activities of cytokines to their endogenous functions within an intact organism is not clearly defined....* Since *most cytokines have ubiquitous biological activities*, their physiologic significance as normal regulators of physiology is often difficult to assess" F. With regard to Wands Factor(7), when challenged, the examiner cited the National Psoriasis Foundation "News & Notices" http://www.psoriasis.org/enbrel.approval.jan02.htm reference. This says flatly, "People with known multiple sclerosis should not take Enbrel." Embrel is an inhibitor of the cytokine α-TNF. That is clear evidence that the prior art now understands that inhibitors of α-TNF actually make matters worse, not better, as would have been expected for the autoimmune disorder multiple sclerosis. These claims read on inhibiting α-TNF, which is one of the most important and is indeed the most studied, of all the cytokines. The point here is that while based on the understanding of the effects of α-TNF, one would expect treatment with an inhibitor of α-TNF to make cellular functioning better for MS, but in fact, it made matters worse. Despite all the research done, more experimentation was clearly needed. Appellants state that this is "not relevant" Why is that not relevant? How is something to be used if it makes the condition worse? This shows the heavy amount of experimentation needed if actual in vivoe, real world results are the opposite of what one expects from in vitro testing. The reference "Centocor Places Congestive Heart Failure Clinical Program On Hold" http://www.jnj.com/news/jnj_news/20020329_0810.htm is cited for support for the statement about CHF, and note the additional statement that "other recent trials have failed to demonstrate that agents that bind TNF can improve the clinical course in these

patients." This shows that even the extensive experimentation that has been done for use of one compound for inhibiting one activity – CHF --- was not sufficient. This shows that extensive experimentation is needed. It may be that something which inhibits α-TNF in the *in vitro* experiments often does not do so in an actual body, it may be that some other mechanism takes place in the body so that the α-TNF does not get suppressed (another cytokine will take up the slack), perhaps there is some other reason. The point here is that extrinsic evidence exists that extensive experimentation is needed.

Enablement to make Solvates

Claims 1-36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for other forms, does not reasonably provide enablement for solvates. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The claims, insofar as they embrace solvates, are not enabled. The evidence of the specification is clear: These compounds do not possess the property of forming solvates; there is no evidence that such compounds even exist.

The numerous examples presented all failed to produce a solvate. The solvents used in the working examples included dimethyl sulphoxide, dimethyl formamide, dichloromethane, pyridine, tetrahydrofuran, acetonitrile, water, ethyl acetate, hexane, toluene, acetic acid, methanol and trimethylamine. Yet, no solvate ever resulted.

Solvates cannot be simply willed into existence. As was stated in *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190 "The specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However ... there is no evidence that such compounds exist... the examples of the '881 patent do not produce the postulated compounds... there is ... no evidence that such compounds even exist." Thus, the Court held lack of enablement because the disclosed procedures in the specification did not even produce the claimed compounds. That is exactly the case here as well: There are a number of examples reported; not one of them produced a solvate.

Appellants state that solvates "could be made using known techniques in the art." One skilled in the art knows that solvates are prepared by exposing the compound to solvent (normally, by preparing, purifying or isolating, in the presence of solvent) and then isolating the solid. If the compound inherently forms solvates, then one will get a solvate; if not, one will not get a solvate. That is, some compounds form solvates; some do not. These compounds, judging by the abundant evidence of the specification, are in the latter category. The specification teaches no methods for overcoming this deficiency, i.e. to force a compound, which does not naturally form one, to form a solvate. The specification does not even seem to be aware of the problem. The remarks do not state how to do this, nor does the examiner know of any such technique.

Appellants state that the examiner "has not explained the basis as to why the compounds of the invention would not form solvates." The examiner does not know why these compounds do not form solvates (especially since some very polar solvents, which are better at forming solvates, were used, e.g. DMSO, DMF, acetonitrile and water). But

that is not the examiner's burden, any more than it was the examiner's burden in *Morton*, to explain why the examples did not produce the postulated compounds.

Appellants argue that "the court in *Morton* did not make a finding ... because there were no working examples." Nor is the examiner making that argument; the examiner has indeed pointed to all the working examples. Instead, Appellants argue, it was because in Morton there was "strong extrinsic evidence that the working examples did not produce the claimed compound having "partial conductivity." The same is true here, with the last four words being changed to "compound in the form of a solvate." The evidence in Morton was expert testimony; the evidence here is Appellants' own specification.

Appellants next argue that the inclusion of solvates is "not uncommon" in patents. Agreed; pharmaceuticals commonly form solvates. These, apparently, do not.

Finally, Appellants argue that "a solvate of the inventive compounds can be made by using known techniques know to persons skilled in the art." One of ordinary skill in the art knows that the method is to expose the compound to the solvent. But since that never worked in all the examples, it is apparent that these compounds simply do not form solvates. The specification teaches no other technique, nor does one of ordinary skill in the art know of one, nor does the rebuttal suggest one.

The New Matter Issue

Claims 1, 2, 18-37 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The second structural formula in claim 1 lacks description in the specification. This is a generic formula where $R_4$ is absent. No such formula exists in the specification, or the original claims; every generic formula requires $R_4$ to be present. Nor does any definition of $R_4$ include that option of being non-existent. Although there are a few such species present, that does not provide description for the genus itself, only the species individually.

The traverse is unpersuasive. Appellants argue that one of ordinary skill in the art would have "necessarily recognized that $R_4$ would not have been present." One of ordinary skill in the art is not going to have "recognized" that a structure that clearly depicts $R_4$ is present actually has $R_4$ as absent. The $R_4$, and the bond to the $R_4$ are not depicted as optional. Therefore, one of ordinary skill in the art would understand that in that structure, the option of there being a double bond from the N to the Carbon to its right cannot exist for that bond, although it can exist for two other bonds in the ring.

Appellants explain the structure's origin as "the original formula was split", but this is not so, since the $R_4$ as absent option was never present. Appellants also state "The original formula included the option to include, or not include, $R_4$." There is no factual basis for that assertion. The "or is absent" is not present in the $R_4$ definition, nor is there the $-(R_4)_{0 \text{ or } 1}$ depiction, the conventional way of saying that something can be present or absent in a structural formula. Thus, neither of the ordinary ways of conveying that a substituent can be present or is absent were used. In fact, nothing was used to convey the fact that $R_4$ was optional.

The additional species that Appellants point to simply do not fall within the genus. It is not uncommon for specification to have species which do not fall within a genus.

The "determining" issue

Claims 19-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Appellant regards as the invention.

The (b) step is unclear in claim 19; it is not consistent with the preamble either. The claim, as set forth by the preamble, is a method of inhibiting, and would appear to be completely accomplished by step (a). But the last step is not an inhibition step, but "determining." Does determining perhaps mean measuring the inhibition after it has occurred? Or is it just observing that the inhibition has occurred, or perhaps just the mental step of knowing, or what?

To give a very simple example, suppose that the inhibition of the cytokine inhibits all the cellular activity in a given cell, i.e. the cell inside someone's body dies. And suppose that the observer does not notice that this one cell has died. The preamble seems to have been met; the activity was inhibited, but step (b), arguably, isn't met because the cell death is unnoticed. Would that fall within the claim or not? It is not clear: the preamble has been met, but the requirements of step (b) apparently have not been met. As stated in *In re Zletz*, 13 USPQ2d 1320, 1322, "An essential purpose of patent examination is to fashion claims that are precise, clear, correct and

unambiguous." This claim is ambiguous. More generally, if the preamble is met because contacting the cell did indeed inhibit some cytokine-mediated activity, but there was no determining (regardless of how "determining" is understood) so that the condition of step (b) is not met, does that fall within the claim or not?

The traverse is unpersuasive. Appellants start by saying that the first step (a) is clear, which is agreed with. Then, Appellants state that determining means "to come to a conclusion", which is a mental step, as noted by the examiner. Appellants, however, given no reasoning why this definition should be used as opposed to another definition, i.e. determining meaning measuring, because, as Appellants themselves note, the term is not defined in the specification. However, even if accepted, the problem of the inconsistency with the preamble remains. It is this inconsistency that the response does not address. The "determining" is a purely mental act, and is the last step, yet the preamble calls solely for a physical act. If the physical act takes place, but the mental act of "coming to a conclusion" does not, it is not clear if the conditions of the claim have been met. Thus, the simple question that the examiner posed is unanswered in the Appeal Brief.

The "cellular process or activity" issue

Claims 19-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Appellant regards as the invention.

The phrase "cellular process or activity" is unclear. It appears in step (b) of claim 19; the preamble has only "an activity" (does not include the word "process"). What is

the difference between process and activity? Isn't every activity a process and vice versa? Is Appellant using some specialized meaning of "process" that is somehow different from "activity"?

Appellants' response points to a distinction which does not appear to be real. Appellants state that "process" means "something going on" and that "activity" means a "a state of being active". In terms of a cell, something going on, and being active, mean exactly the same thing. If a cell is active, it means that something is going on. If something is going on in the cell, that means that the cell is active. In other words, activity in a cell means that a cellular process is going on, and vice versa. Thus, Appellants are making a distinction without a difference.

Appellants state that it is "only the examiner's personal opinion that the terms mean the same thing". This is not a matter of the examiner's personal opinion of the meaning of the terms; the examiner accepts both the asserted definition for process and the asserted definition for activity. However, the claims fail to particularly point out and distinctly claim if Appellants present definitions for the terms and insist that they are (somehow) different, and yet the meanings are the same. Appellants have in fact presented no actual explanation as to what the differences are between the two terms.

To resolve this matter quickly, Appellants had been asked to provide a single example of a cellular process which is not an activity, or a cellular activity which is not a process. Either one of these would demonstrate that the terms are, as Appellants insist, different. No such example has been presented.

The scope of claims 23 and 24

Claims 23-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Appellant regards as the invention.

The scope of claims 23 and 24 is unclear. Claim 23 limits claim 19 by saying that "said activity is the secretion of proinflammatory cytokines." Claim 24 is the same, but for anti-inflammatory. An example of a proinflammatory cytokine is α-TNF. An example of antiinflammatory cytokine is IL-10. An example of a cytokine which possesses both pro-inflammatory and anti-inflammatory activities is TGF-beta-1. Some cytokines are known to be neither. For most cytokines, so little is known that it is unclear which category, if any, the cytokine belong in. The problem, thus, is that there is no even semi-complete standard list of pro-inflammatory and anti-inflammatory cytokines that one can consult.

To figure out whether a method fell within claim 23, one would contact a living cell with a compound of claim 1, and then see if there was any change in the secretion of proinflammatory cytokine α-TNF. If not, one would then move on to other known proinflammatory cytokines such as IL-1α, IL-1β, IL-6, IL-8, IL-18, MIP-1a, IFN-γ, etc. Then one would move on to the hundreds of cytokines for which it is not known whether or not they were proinflammatory, conduct a research project for each one to find out it is was proinflammatory, then, if proinflammatory, do the test with the compound of claim 1. The determination of the properties of a cytokine is a major undertaking, and for the great majority, very little is known. And note that the

compound does not itself have to inhibit the secretion of e.g. α-TNF. It could stimulate the production of something else which in turn inhibits the secretion of α-TNF, or it could inhibit the production of something which stimulates the secretion of α-TNF. In fact, the regulation of cytokines is based on all manner of feedback mechanisms built into an entire network of intercellular signals, as the specification recognizes on page 2.

The "Thioalkyl" issue

Claims 1-7 and 18-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Appellant regards as the invention

"Thioalkyl", which occurs in the definition of $R_2$ and $R_3$, is not standard nomenclature. Thio as a generic prefix simply indicating the presence of sulfur. "Thioalkyl" could have a number of possible meanings. It is possible that the term refers to HS-alkyl-, which is properly called the mercaptoalkyl group. It is also possible that it is intended to refer to the alkyl-S- group, which is properly called the alkylthio group. It could possibly refer to the replacement of a carbon in an alkyl with a Sulfur, e.g. $CH_3$-S-$CH_2$-. Another alternative is that the sulfur could be a double bonded substituent (rather than a single bonded one as seen in mercaptoalkyl), e.g. $CH_3$-C(=S)-$CH_2$-, properly called the thioxoalkyl. Alternatively, there might be some different letters missing, so that what was intended was thiophenylalkyl, i.e. the alkyl is substituted by thiophene, or possibly thionoalkyl, i.e. alkyl substituted by =C=S, the thiono group. This specification gives no clear evidence as to which of these plausible

choices was originally intended, as the extensive list of definitions does not cover this term at all. As stated in *In re Zletz*, 13 USPQ2d 1320, 1322, "An essential purpose of patent examination is to fashion claims that are precise, clear, correct and unambiguous." This term is clearly ambiguous.

The traverse begins by apparently agreeing that this is a prefix meaning the presence of sulfur. Beyond that, things are less clear. Originally, Appellants had said that "it is an alkyl containing a sulfur atom." That is impossible. An alkyl cannot contain a Sulfur atom. Now, Appellants state that it is "an alkyl group which contains a thio group as a substituent." But this just begs the question, since there is no such substituent as "a thio group". Appellants now present as an example the HS-$CH_2$-$CH_2$- group, so that this "thio group" is the HS- or mercapto group. No reason is presented as to why this choice among many would be selected. In fact, this specification actually mitigates, albeit weakly, against this choice. In the definition of the R1 variable, the 8th choice is listed as "sulfhydryl (mercapto)". Both of these words mean the same thing, the HS- group. Given the fact that both of these unambiguous terms are already being used by this application to denote the HS- group, it would seem (a little) unlikely that the specification would then use the generic "thio" to also denote the same group. That is, given the context of a specification which already uses the correct terms sulfhydryl and mercapto, we would expect that if the HS-$CH_2$-$CH_2$- group really were intended, that it would have been called the mercaptoalkyl, or the sulfhydrylalkyl group. Since it wasn't, that (somewhat) implies that mercaptoalkyl wasn't actually intended. Applicants have cited a US patent which used the term, but present no arguments as to how that different specification provides guidance on how the term is used in this specification.

*(11) Response to Appendix References*

Appellants have provided assorted references with the Appeal Brief in Appendix B, D and E. None of these references are of record and will not be specifically considered.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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